Gene-trapped mouse embryonic stem cell-derived cardiac myocytes and human genetics implicate AKAP10 in heart rhythm regulation.

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Authors: Whittemore G Tingley, Ludmila Pawlikowska, Jonathan G Zaroff, Taeryn Kim, Trieu Nguyen, Stephen G Young, Karen Vranizan, Pui-Yan Kwok, Mary A Whooley, Bruce R Conklin

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Public Summary:

Scientific Abstract:
Sudden cardiac death due to abnormal heart rhythm kills 400,000-460,000 Americans each year. To identify genes that regulate heart rhythm, we are developing a screen that uses mouse embryonic stem cells (mESCs) with gene disruptions that can be differentiated into cardiac cells for phenotyping. Here, we show that the heterozygous disruption of the Akap10 (D-AKAP2) gene that disrupts the final 51 aa increases the contractile response of cultured cardiac cells to cholinergic signals. In both heterozygous and homozygous mutant mice derived from these mESCs, the same Akap10 disruption increases the cardiac response to cholinergic signals, suggesting a dominant interfering effect of the Akap10 mutant allele. The mutant mice have cardiac arrhythmias and die prematurely. We also found that a common variant of AKAP10 in humans (646V, 40% of alleles) was associated with increased basal heart rate and decreased heart rate variability (markers of low cholinergic/vagus nerve sensitivity). These markers predict an increased risk of sudden cardiac death. Although the molecular mechanism remains unknown, our findings in mutant mESCs, mice, and a common human AKAP10 SNP all suggest a role for AKAP10 in heart rhythm control. Our stem cell-based screen may provide a means of identifying other genes that control heart rhythm.

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